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(71) Applicant(s)
The University Of Nottingham

(Incorporated in the United Kingdom)

Lenton Lodge, University Park, NOTTINGHAM, NG7 2RD, United Kingdom

(72) Inventor(s)
Anthony Robert Lyons
Sharon Patricia Mary Crouch
David James Phipps
Andrew Wilcock

(74) Agent and/or Address for Service
Swindell & Pearson
48 Friar Gate, DERBY, DE1 1GY, United Kingdom

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(56) Documents Cited
WO 96/23505 A1 US 4942157 A US 4634691 A
CAPLUS Abstract Acc. No. 1994:208165 & Life Sci.(1994), 54(14) p229-234. CAPLUS Abstract Acc. No. 1993:139456 & Drug Dev. Res. (1993) 28(1) p47-55. CAPLUS Abstract Acc. No. 1988:156353 & Virchows. Arch. B (1988), 54(4), p241-5. CAPLUS Abstract Acc. No. 1986:81724 & Ann Rheum. Dis. (1986) 45(1), p67-74. CAPLUS Abstract Acc. No. 1979:29014 & DE 2813121 (PROCTOR & GAMBLE)

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UK CL (Edition O) A5B BHA BJA
INT CL^6 A61K 31/66
ONLINE: CAS & STN INDEX (PHARMACOLOGY)

(54) Bisphosphonates as anti-inflammatory agents

(57) The use of a bisphosphonate, and in particular ibandronate (formerly known as BM21.0955) for the preparation of an agent for the treatment of diseases of chronic immune system activation and also for the preparation of an anti-inflammatory agent for the treatment of inflammatory disorders.

GB 2 312 165 A

At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

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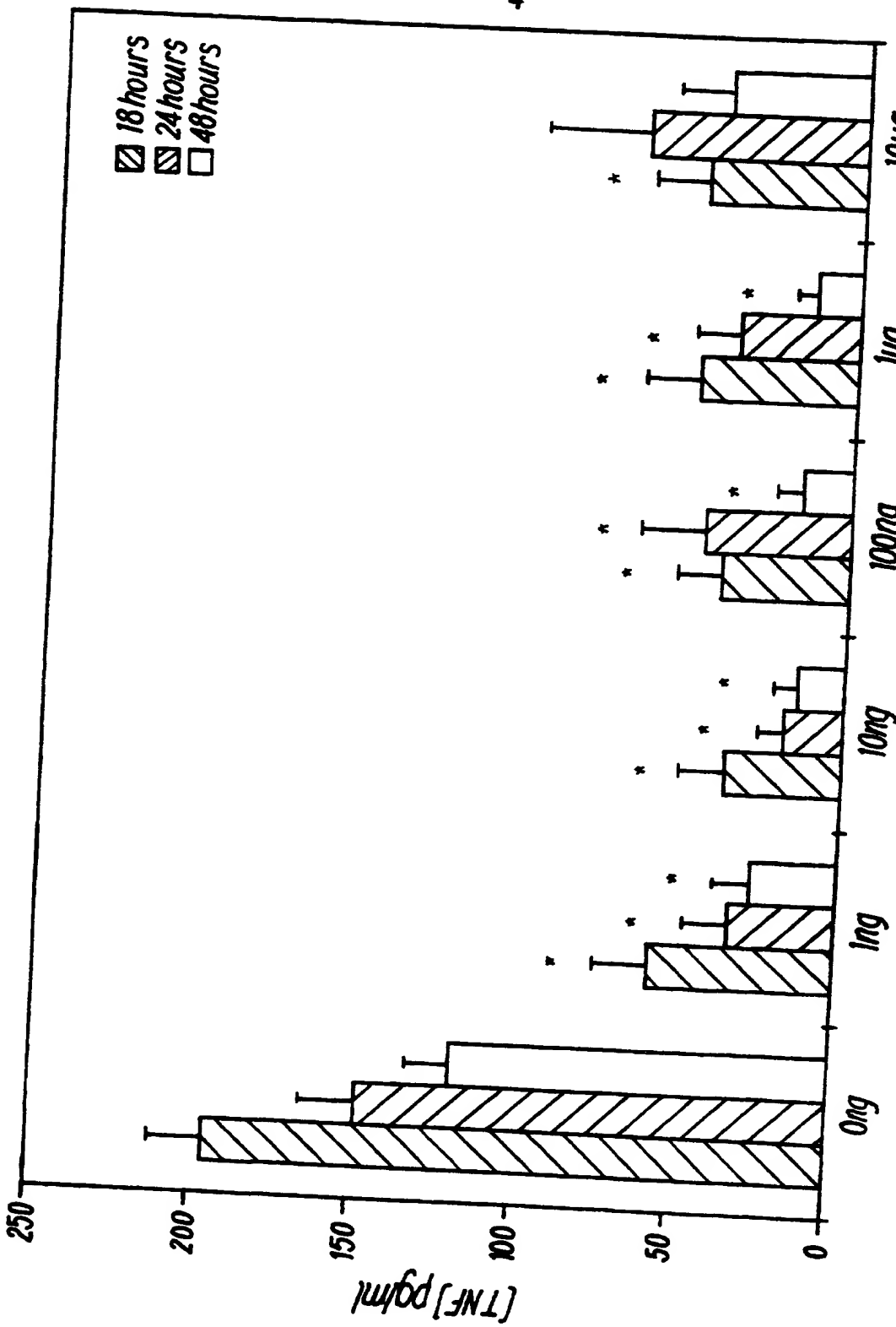

Fig. 1

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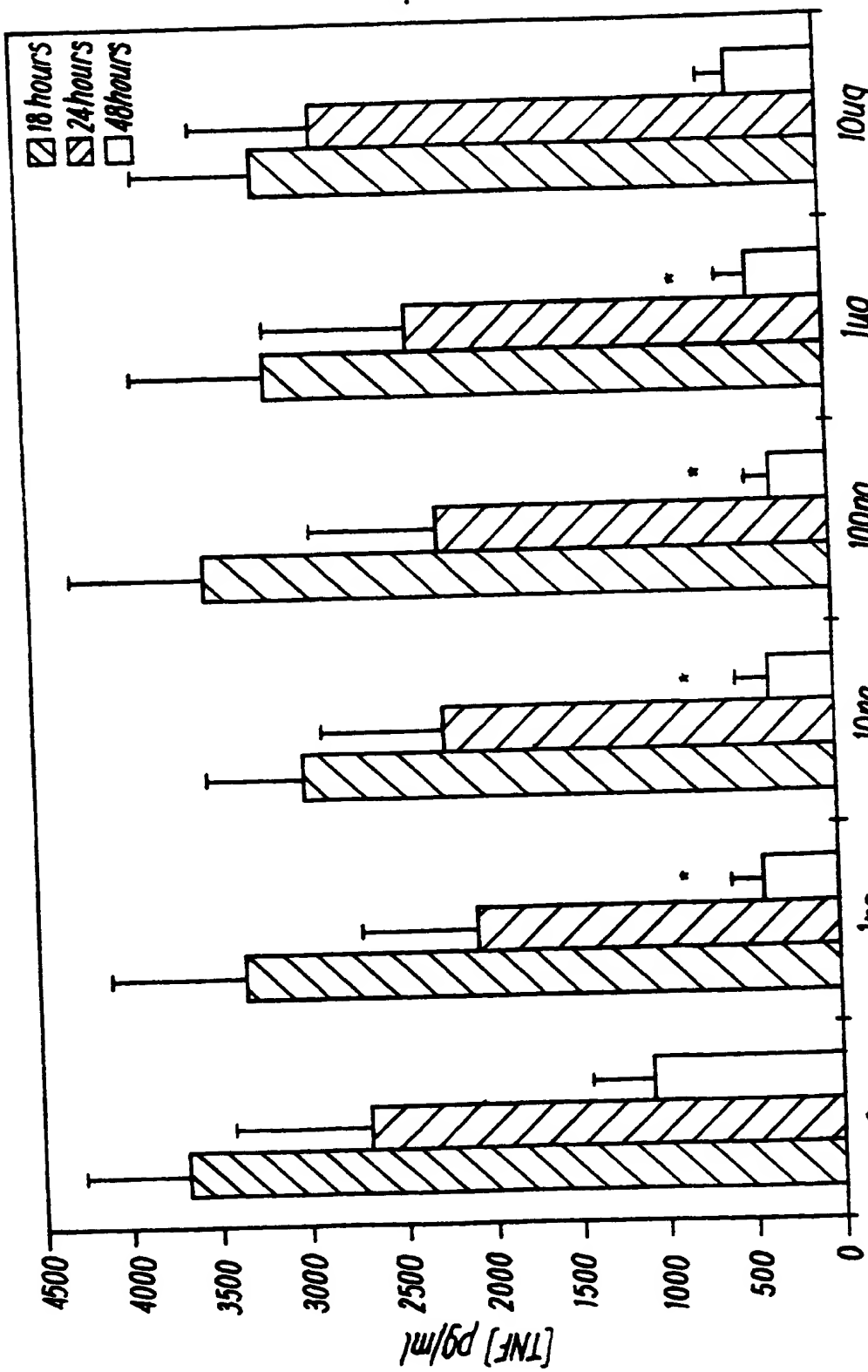

Fig. 2

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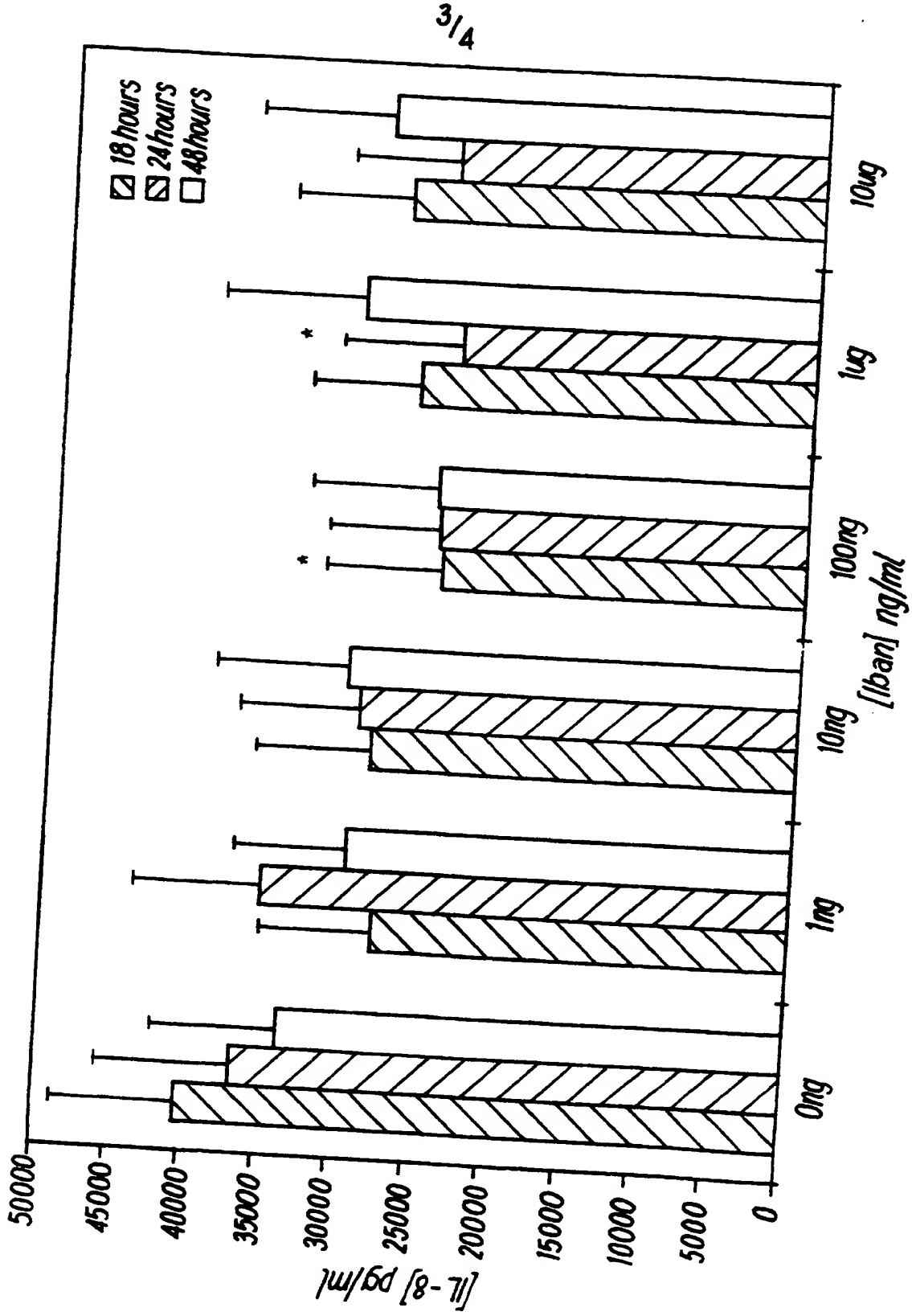

Fig 3

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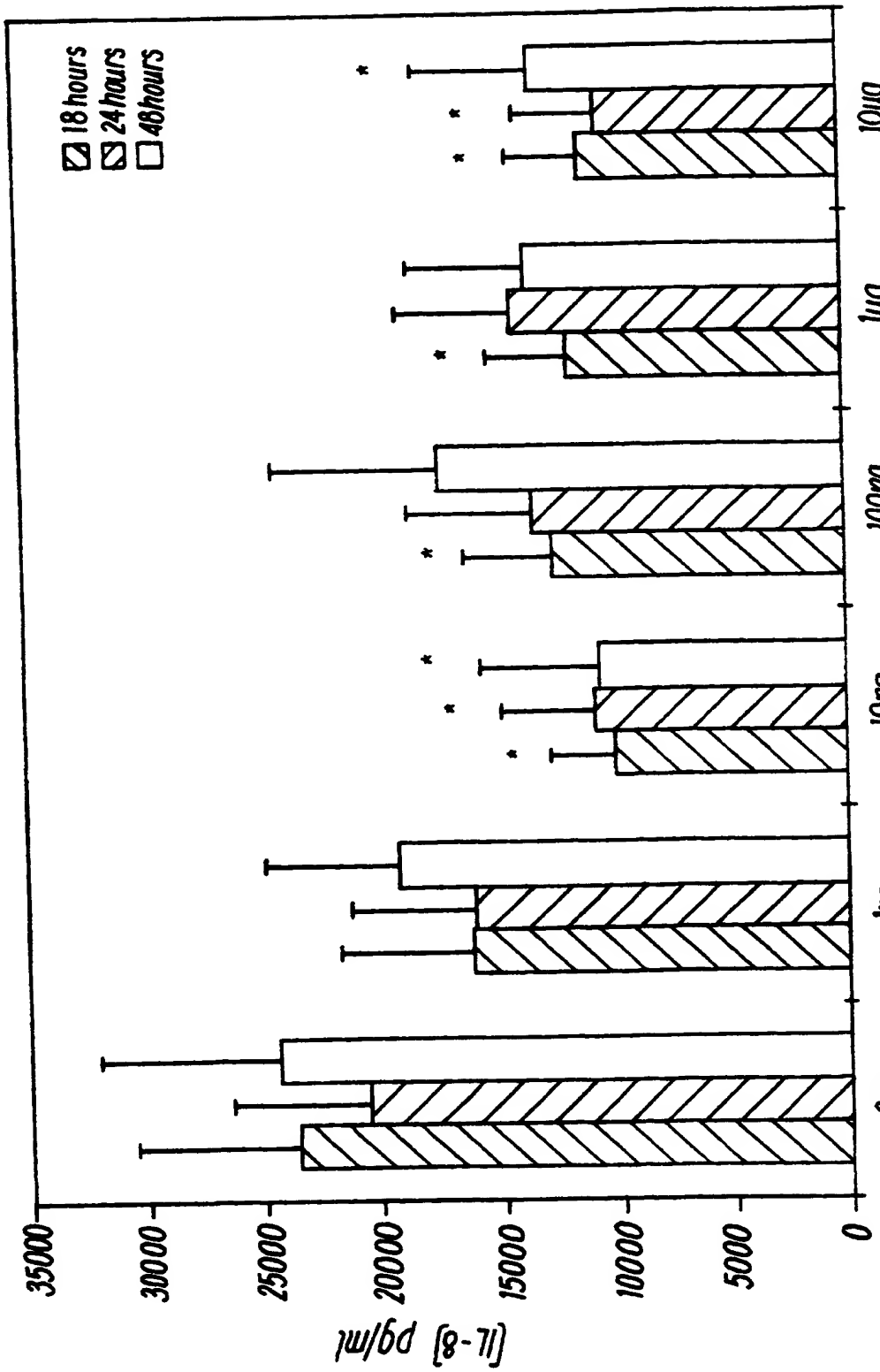

Fig. 4

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Bisphosphonates as Anti-Inflammatory Agents

The present invention relates to bisphosphonates as anti-inflammatory agents, and particularly but not exclusively to ibandronate as an anti-inflammatory agent.

Diseases of chronic immune system activation, such as cancer, Multiple Sclerosis (MS) and Acquired Immune Deficiency Syndrome (AIDS) cause localised inflammation of body tissue. This inflammation is mediated by cells of the immune system, including lymphocytes and macrophages, producing biochemicals, such as cytokines (Interleukins, Tumour Necrosis Factor) at the diseased site. These biochemicals act as chemical signals which attract further cells to the site, resulting in inflammation and often associated symptoms such as severe pain.

One example of a disease causing chronic immune system activation is cancer, in which tumour associated macrophages are involved in tissue remodelling and inflammation, and through the action of a number of cytokines released thereby control neovascularisation, tumour growth and stroma formation. Macrophages are recruited from the circulation in response to chemotactic factors such as monocyte chemotactic protein 1 (MCP-1) released by the diseased tissue. Another member of the chemokine family is Interleukin-8 (IL-8), a neutrophil chemo-attractant. Secretion of this cytokine by tumour associated macrophages causes the influx of neutrophils, which cells are then capable of producing an accute inflammatory reaction through the release of proteinases and toxic oxygen metabolite. Neutrophils are also capable of the *de novo* biosynthesis of cytokines, in particular Interleukin-1 (IL-1). Interleukin-1 induces biochemical and cellular changes characteristic of the types of inflammation and tissue remodelling observed in joint destruction diseases. Interleukin-1 has also been shown to be a potent agonist for Interleukin-8 release from peripheral blood mononuclear cells. In addition to being a potent neutrophil chemotaxin Interleukin-8 has also been shown to play a role in angiogenesis, and has been implicated in promoting tumour growth and metastases through neovascularisation.

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Conventionally, diseases of chronic immune system activation are frequently treated with systemic corticosteroids, cyclophosphamide or cyclosporin. The use of these amino suppressive drugs is complicated by adverse reactions including neutrophenia, lymphopenia, monocytopenia. In addition to a reduction in the number of these immune cells, their function is also decreased. Moderate side effects of these drugs include abdominal pain, nausea and vomiting. Devasting side effects of prolonged immunosuppressive therapies include infertility, aseptic necrosis, teratogenesis and vertebral collapse. In addition, prolonged use of these drugs frequently does not alter the course or eventual outcome of the disease; rather, they treat symptoms of relapse or exacerbation.

It is therefore an object of the present invention to provide an improved anti-inflammatory agent to thereby reduce inflammation in conditions of chronic immune system activation, and other inflammatory conditions such as rheumatoid arthritis.

According to the present invention there is provided the use of a bisphosphonate for the preparation of an agent for the treatment of chronic immune system activation disorders.

The invention also provides the use of a bisphosphonate for the preparation of an anti-inflammatory agent for the treatment of disorders.

According to a further aspect of the present invention there is provided the use of ibandronate for the preparation of an agent for the treatment of chronic immune system activation disorders.

According to a further aspect of the present invention there is provided the use of ibandronate for the preparation of an anti-inflammatory agent for the treatment of inflammatory disorders.

The invention further provides for the use of bisphosphonates to

modulate immune cell activity, such as lymphoctye and macrophage cell activity. Preferably bisphosphonate is used to inhibit inflammatory agent production, such as cytokine production and desirably including Interleukin, such as Interleukin-1.

Preferably the bisphosphonate is used *in vitro*, and preferably comprises ibandronate.

A still further aspect of the present invention provides for the use of bisphosphonates, in particular ibandronate to inhibit pro-inflammatory cytokine production and/or activity.

The invention further provides a pharmaceutical composition comprising a bisphosphonate and a physiologically acceptable excipient or carrier.

The bisphosphonate preferably comprises ibandronate.

An embodiment of the present invention will now be described by way of example only, with reference to the accompanying drawings. The drawings all comprise graphs, showing:

Fig. 1 - the effect of ibandronate on TNF secretion (No LPS);

Fig. 2 - the effect of ibandronate on TNF secretion (10pg/ml LPS);

Fig. 3 - the effect of ibandronate on IL-8 production : 10pg/ml LPS; and

Fig. 4 - the effect of ibandronate on IL-8 secretion (No LPS).

The present invention principally provides for the use of a bisphosphonate, and in particular ibandronate (formerly known as BM21.0955) for the preparation of an agent for the treatment of diseases of chronic immune system activation and also for the preparation of an anti-inflammatory agent

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for the treatment of inflammatory disorders.

Ten patients were identified with advanced metastatic prostate carcinoma and bone pain due to lesions deposited in the bone. From peripheral blood, mononuclear cells were extracted and cultured (using a well recognised standard technique) with or without the presence of bacterial lipopolysaccharide (LPS) - a potent stimulator of these cells. In addition, varying concentrations of ibandronate were also added to the culture medium.

At varying time points, the cell cutlures were analyzed for the production of Interleukin 1 (IL-1), Intereukin -1 receptor antagonist (IL-1ra), Tumour Necrosis Factor (TNF), soluble TNF receptor inhibitor (sTNFRI) and Interleukin-8 (IL-8). Ibandronate did not induce significant inhibition of IL-1 in the presence or absence of LPS. Neither was there a significant effect of ibandronate on IL-1ra release.

Ibandronate was seen to inhibit the spontaneous production of TNF however in the presence of LPS there was only significant inhibition after 48 hours of culture which is at the limit for cell viability in this cutlure technique. (Figs. 1 and 2). Ibandronate inhibited IL-8 secretion in a concentration dependent fashion in the presence or absence of LPS. (Figs. 3 and 4). No effect was shown upon the secretion of soluble TNF receptor inhibitor (sTNFRI).

Ibandronate may act as an anti-inflammatory agent through its inhibitory effects upon IL-8. This may prevent recruitment and activation of inflammatory cells. IL-8 is a potent stimulator of angioneogenesis (new blood vessel formation) at tumour sites and this may be effective in controlling metastatic seeding or growth. No change in the response of the cells was noted when they were first stimulated with LPS. This would suggest that responses to infective processes may be unimpaired and inhibition of the cytokine response would not render subjects immunodefficient.

Ibandronate therefore appears to specifically target the TNF and

Interleukin-8 pathway to inhibit the production of these pro-inflammatory cytokines, and since cytokines are fundamental to inflammation thereby obviate or mitigate chronic immune system activation inflammation. This not only provides for alleviation of symptoms of many chronic immune system activation disorders, such as cancer, MS and AIDS, but may also provide a basis for keeping such diseases in check or providing a complete cure. Ibandronate can also be used to treat other inflammatory diseases such as rheumatoid arthritis, and also to prevent metastases of cancer.

The clinical use of ibandronate has shown that it has minimal side effects, the only known side effect consisting solely of morning fever. Thus, the use of ibandronate in accordance with the present invention will not be associated with the adverse reactions associated with the conventional use of immune suppressants.

Thus, it will be appreciated that the use of bisphosphonates, and in particular ibandronate as an anti-inflammatory agent, and for the preparation of an agent for the treatment of chronic immune system activation disease, via the modulation of the activity and cytokine production of immune cells, including lymphocytes and macrophages offers many advantages over known drugs. Since activated macrophages, lymphocytes and pro-inflammatory cytokines are involved in the pathogenesis and generation of symptom burden in disease of chronic immune system activation, ibandronate provides effective treatment for these diseases and their symptoms.

It is to be appreciated that the use of bisphosphonates and in particular ibandronate, as agents to prevent or reduce inflammation caused by other disorders, such as arthritis, is within the scope of this invention. Further, the use of bisphosphonates, and particularly ibandronate to inhibit or prevent metastases in cancer conditions is also within the scope of this invention.

Whilst endeavouring in the foregoing specification to draw attention to those features of the invention believed to be of particular importance it should

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be understood that the Applicant claims protection in respect of any patentable feature or combination of features hereinbefore referred to and/or shown in the drawings whether or not particular emphasis has been placed thereon.

CLAIMS

1. The use of a bisphosphonate for the preparation of an agent for the treatment of chronic immune system activation disorders.

2. The use of a bisphosphonate for the preparation of an anti-inflammatory agent for the treatment of disorders.

3. The use of ibandronate or an active derivative thereof for the preparation of an agent for the treatment of chronic immune system activation disorders.

4. The use of ibandronate or an active derivative thereof for the preparation of an anti-inflammatory agent for the treatment of inflammatory disorders.

5. The use of bisphosphonates to modulate immune cell activity, such as lymphoctye and macrophage cell activity.

6. The use of bisphosphonate as claimed in any preceding claim, in which bisphosphonate is used to inhibit inflammatory agent production, such as cytokine production.

7. The use of bisphosphonate as claimed in any preceding claim, in which the bisphosphonate inhibits Interleukin, such as Interleukin-1.

8. The use of bisphosphonate as claimed in any preceding claim, in which the bisphosphonate is used *in vitro*.

9. The use of bisphosphonate as claimed in claim 8, in which the bisphosphonate comprises ibandronate or an active derivative thereof.

10. The use of bisphosphonates, in particular ibandronate or an active derivative thereof to inhibit pro-inflammatory cytokine production and/or activity.

11. A pharmaceutical composition comprising a bisphosphonate and a physiologically acceptable excipient or carrier.

12. An anti-inflammatory agent comprising bisphosphonate.

13. A pharmaceutical composition as claimed in claim 11 or 12, in which the bisphosphonate comprises ibandronate or an active derivative thereof.

14. The use of bisphosphonate substantially as hereinbefore described with reference to the accompanying drawings.

15. The use of ibandronate or an active equivalent thereof as hereinbefore described with reference to the accompanying drawings.

16. A pharmaceutical composition as hereinbefore described with reference to the accompanying drawings.

17. An anti-inflammatory agent as hereinbefore described with reference to the accompanying drawings.

18. Any novel subject matter or combination including novel subject matter disclosed, whether or not within the scope of or relating to the same invention as any of the preceding claims.

The Patent Office

9

Application No: GB 9707570.9
Claims searched: 1-4, 11-13, 16 & 17

Examiner: Dr J. P. Bellia
Date of search: 26 June 1997

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): A5B (BHA, BJA)

Int Cl (Ed.6): A61K 31/66

Other: ONLINE: CAS & STN INDEX (PHARMACOLOGY)

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
P,X	WO 96/23505 A1 (TERONEN) see claims 1, 5, 6 & 17; page 5 line 20-32 & page 7 line 19-25 & page 8 line 32- page 9 line 23	1-4 & 11-13
X	US 4942157 (GALL & BOSIES) see claims 1 & 2	11 & 13
X	US 4634691 (HEDGLIN & MARTODAM) see column 2 line 24-32 & column 7 line 16-21	1, 11
X	CAPLUS Abstract Accession No. 1994:208165 & Life Sciences 54(14), (1994), p229-234. Monkkonen *et al.* Clodronate inhibits LPS-stimulated IL-6 and TNF production. see abstract	1, 2, 11 & 12
X	CAPLUS Abstract Accession No. 1993:139456 & Drug Dev. Res. 28(1), (1993), p47-55. Dunn *et al.* Investigation of the acute and chronic anti-inflammatory properties of diphosphonates. see abstract	1, 2 & 12
X	CAPLUS Abstract Accession No. 1988:156353 & Virchows. Arch. B 54(4), (1988), p241-45. Van Rooij *et al.* Elimination of macrophage tumor cells using liposome encapsulated diphosphonate see abstract	1, 2, 11 & 12

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

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The Patent Office

10

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Date of search: 26 June 1997

Category	Identity of document and relevant passage	Relevant to claims
X	CAPLUS Abstract Accession No. 1986:81724 & Ann. Rheum. Dis. 45(1), (1986), p67-74. Barbier *et al.* Studies on the chronic phase of adjuvant arthritis effect of SR 41319, a new diphosphonate. see abstract	2 & 12
X	CAPLUS Abstract Accession No. 1979:29014 & DE 2813121 (PROCTOR & GAMBLE) see abstract	2, 11 &12

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Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

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